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A Randomised Open-Label Trial Comparing Long-term Sub-Cutaneous Low-Molecular-weight Heparin Compared with Oral-Anticoagulant Therapy in the Treatment of Deep Venous Thrombosis

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Low-molecular-weight heparin;
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Abstract *Objective:* To evaluate whether low-molecular-weight heparin (LMWH) could be equally (or more) effective than oral anti-vitamin-K agents (AVK) in the long-term treatment of deep venous thrombosis (DVT).
Design: A randomised, open-label trial.
Material and methods: In this trial, 241 patients with symptomatic proximal DVT of the lower limbs confirmed by duplex ultrasound scan were included. After initial LMWH, patients received 6 months of treatment with full therapeutic dosage of tinzaparin or acenocoumarol. The primary outcome was the 12-month incidence of symptomatic recurrent venous thrombo-embolism (VTE). Duplex scans were performed at 6 and 12 months.
Results: During the 12-month period, six patients (5%) of 119 who received LMWH and 13 (10.7%) of 122 who received AVK had recurrent VTE ($p = 0.11$). In patients with cancer, recurrent VTE tended to be lower in the LMWH group (two of 36 [5.5%]) vs. seven of 33 [21.2%]; $p = 0.06$). One major bleeding occurred in the LMWH group and three in the AVK group. Venous re-canalisation increased significantly at 6 months (73.1% vs. 47.5%) and at 12 months (91.5% vs. 69.2%) in the LMWH group.

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Conclusions: Tinzaparin was more effective than AVK in achieving re-canalisation of leg thrombi. Long-term tinzaparin was at least as efficacious and safe as AVK for preventing recurrent VTE, especially in patients with cancer.

Low-molecular-weight heparin (LMWH) has a number of theoretical advantages over oral-anticoagulant therapy. Compared to vitamin-K antagonists, LMWH has more stable pharmaco-kinetic properties and fewer drug interactions.[1] Consequently, weight-based dosing of this agent produces a predictable anticoagulant effect that does not require routine laboratory monitoring.

The role of LMWH as an alternative to oral anticoagulation in the outpatient DVT treatment for the prevention of recurrent venous thrombo-embolism (VTE) has been evaluated in several clinical trials.[2–8] These trials primarily included patients without cancer and used prophylactic doses of LMWH for extended treatment rather than full therapeutic doses that are used for the initial treatment of VTE.

A systematic evaluation of these studies found a non-significant reduction in the risk of recurrent VTE in favour of LMWH and concluded that there is little evidence to suggest whether long-term LMWH treatment is as effective as vitamin-K antagonist treatment.[9] The authors observed that the prophylactic LMWH doses used in some of these trials may have resulted in inadequate therapy.[6,8]

Subsequently, several clinical trials showed that long-term LMWH was more effective than anti-vitamin-K agents (AVK) for preventing recurrent VTE without increased bleeding[10–13] and it is now recommended in most international guidelines.[14] Whether this benefit applies to other patient groups with deep vein thrombosis (DVT) is uncertain. Because of the uncertainty, vitamin-K antagonist treatment is still the treatment of choice in the prevention of recurrent symptomatic VTE.[8] However, majority of previous investigations that compared long-term LMWH with oral anticoagulants did not use ultrasonographic endpoints, leading to questions about the resolution of thrombi and the prevention of valve insufficiency.[15]

We conducted a randomised, open-label clinical trial in patients with acute DVT to evaluate clinical efficacy as well as the resolution of thrombi with long-term therapeutic doses of tinzaparin compared with the usual care consisting of tinzaparin and long-term acenocoumarol.

Patients and Methods

Study design

We conducted an open-label prospective randomised clinical trial to compare sub-cutaneous LMWH (tinzaparin) administered for 6 months with initial treatment using sub-cutaneous LMWH followed by oral anticoagulants given for a similar period of time in patients with proximal venous thrombosis. Two centres in Spain participated in the trial. The protocol was approved by the institutional review board at each centre and by the regulatory authorities. Written, informed consent was obtained from all patients. The primary outcome measurements were those of the incidence of first episode of objectively documented symptomatic DVT or pulmonary embolism at 6 months and 1 year.

Patient selection

Consecutive, symptomatic patients of either sex and over 18 years of age, who had been referred to the Vascular Surgery Department of the hospital with a first episode of acute proximal-vein thrombosis of the lower limbs (onset of symptoms less than 2 weeks) documented by compression ultrasonography, were enrolled in the study from January 2002 to January 2005.

Patients were excluded if they had any of the following conditions: pulmonary embolism requiring thrombolytic therapy, surgical thrombectomy or vena cava interruption, contraindication to anticoagulant treatment (active bleeding, severe blood pressure or allergy to the study drugs), platelet count lower than $100 \times 10^3\ \mu l^{-1}$ or haemoglobin concentration lower than $7\ g\ dl^{-1}$, severe renal failure necessitating dialysis, pregnancy; a history of heparin-associated thrombo-cytopenia; surgery within the previous 14 days, lumbar puncture within the previous 24 h and those receiving oral-anticoagulant treatment or anti-platelet drugs for other conditions unable to discontinue this medication during the treatment interval. Eligible patients were excluded if they had received heparin, LMWH or oral-anticoagulant therapy for more than 2 days.

Treatment

All patients were given tinzaparin (innohep®, LEO Pharma A/S) sub-cutaneously in a fixed dose of 175 IU anti-Xa per kg of body weight once daily. The patients randomised to tinzaparin received this regimen for 6 months without dosage adjustments. The patients randomised to oral anticoagulants were given 3 mg of acenocoumarol orally which was subsequently adjusted to achieve a regular international normalised ratio (INR) of between 2 and 3 for 6 months. In these patients, tinzaparin was given until the INR reached at least 2 on two consecutive measurements. Thereafter, INR monitoring was performed by the haematologists every month until completion of therapy.

Duplex ultrasonography

Diagnosis was established by duplex ultrasonography using linear array 5—10 MHz (ATL-Ultramark 5000 and Aloka 6000). The deep veins were examined using compression by the transducer on B-mode in the cross-sectional view. Colour flow was used to detect luminal feeling defects and Doppler tracings were also obtained. Diagnosis was established by using the following ultrasound criteria: (1) no

collapse or partial collapse of the vein lumen at transducer compression; (2) thrombus visualisation within vein lumen; (3) absence of spontaneous venous flow; (4) absence of Doppler signal and (5) increase in vein diameter.

At least two of the above criteria had to be present before a diagnosis of DVT was made.

The compression method was used to assess thrombus resolution. The vein segment under examination was classified as 'totally re-canalised' when it was compressible with gentle transducer pressure and showed normal flow with colour-flow imaging; 're-canalised' if the vein wall could be approximated, even if not completely, and flow was evident with colour-flow imaging and 'occluded' if the segment could not be compressed at all, with high echoes in the lumen, irregular thick wall and with no flow on colour-flow imaging.

Follow-up and surveillance

All patients were instructed to come to the hospital immediately if they had symptoms or signs suggestive of recurrent DVT, pulmonary embolism or bleeding. All patients who were presented with symptoms or signs of recurrent VTE underwent ultrasonography. In addition, a thorough clinical examination, as well as an ultrasound assessment of the venous system of both lower limbs was performed on all patients who attended routine visits to the clinic at 1, 6 and 12 months after entry.

All objective diagnostic tests were interpreted by specialists who were not involved in the study. The haematologists were responsible for monitoring the oral-anticoagulation therapy. The vascular surgeon, who performed the serial duplex scan, did not know the treatment allocation. D-dimer testing (IL test D-dimer on the ACL 9000 automated coagulation analyser) was performed at baseline and about a month after the patients completed 6 months of therapy with tinzaparin or acenocoumarol. D-dimer values above 235 ng ml^{-1} were classified as abnormal.

Clinical assessments

The primary outcome measurements were the first episode of objectively documented symptomatic DVT or pulmonary embolism at 6 months and 1 year. Recurrent venous thrombosis was diagnosed when a previously compressible proximal-vein segment or segments were no longer compressible on ultrasonography. In patients with clinically suspected pulmonary embolism, the diagnosis was confirmed by a high-probability lung scan finding, an abnormal perfusion scan with documented new DVT or a spiral CT scan showing thrombus in the pulmonary arteries.

The primary safety endpoint was the occurrence of major bleeding during the 6-month treatment interval. Bleeding was classified as major if it was overt and associated with a fall in the haemoglobin level of 2 g dl^{-1} or more, resulted in the transfusion of two or more units of blood, was retroperitoneal, occurred into a major joint or was intra-cranial.

Statistical analysis

A sample size of 121 patients in each treatment group was initially chosen to provide 80% power for a two-sided test ($\alpha = 0.05$) to detect a 14% reduction in recurrences from the 11% experienced in a previous trial.

Baseline comparability was assessed by the tabulation of patient characteristics. All study data were summarised by means of appropriate descriptive statistics. The following tests were used to compare treatment groups at baseline: Fisher's exact test for categorical variables, Student's *t*-test for continuous variables and Mann–Whitney test for ordinal variables. The Kaplan–Meyer method was used to estimate the survival function for time-to-event variables and the log-rank test was used to compare both treatments. A multivariate step-wise regression model was used to identify independent variables that could influence the percentage of recurrences of DVT in both groups. The analysis was performed using SPSS v.11, and the level of significance for all tests was established at the 0.05 level (two sided).

Results

Study population

The study population consisted of 241 consecutive patients, who were recruited from two centres and randomised to either LMWH therapy sub-cutaneously (119 patients) or LMWH followed by acenocoumarol (122 patients). The groups were comparable at entry (Table 1). The groups were also similar with respect to the likely aetiology of their DVT. Two patients from each group died during the follow-up period due to cancer. The rest of the patients randomised and completed the 12-month protocol successfully.

Recurrent VTE

Five of 119 patients (4.2%) receiving LMWH and seven of 122 patients (5.7%) receiving LMWH followed by acenocoumarol had new symptomatic, objectively documented venous thrombo-embolic events during the 6-month treatment interval ($p = 0.6$). Two patients (one from each group) who developed symptoms of pulmonary embolism on the same day of randomisation were also included in the analysis. At the completion of 1 year, six patients assigned to LMWH (5%) and 13 patients assigned to LMWH and acenocoumarol (10.65%) had new episodes of symptomatic VTE documented by objective testing ($p = 0.11$; 95% CI: −12.4% to 1.1%) (Table 2, Fig. 1a). A patient in the AVK group had two recurrences on days 6 and 300, but only the first event was considered for this analysis.

In the cancer population, two patients receiving LMWH (5.5%) and three patients receiving LMWH followed by acenocoumarol (9.1%) had new episodes of VTE during the 6-month treatment interval ($p = 0.58$; 95% CI: −15.9% to 8.8%). At 1 year (Fig. 1b), two patients in the LMWH group (5.5%) and seven patients in the LMWH followed by long-term acenocoumarol group (21.2%) had new episodes of symptomatic VTE ($p = 0.06$; 95% CI: −31.5% to 0.17%).

Sub-analysis of recurrent VTE after the treatment period (Fig. 1a) showed that one patient who received LMWH (0.85%) and seven patients who received acenocoumarol (5.7%) had new episodes of VTE up to 1 year ($p = 0.03$; 95%

Table 1 Clinical characteristics of patients with proximal venous thrombosis treated with long-term low-molecular-weight heparin or oral-anticoagulant therapy

Characteristic	All patients		Patients with cancer	
	Acenocoumarol	LMWH	Acenocoumarol	LMWH
	$N = 122$	$N = 119$	$N = 33$	$N = 36$
	No. of patients (%)		No. of patients (%)	
Age (year ± SD)	61.3 ± 16.2	58.9 ± 17.6	64.7 ± 15.2	59.8 ± 15.5
Sex (M, %)	70 (57.4)	64 (53.8%)	20 (60.6)	18 (50)
Risk factors				
Thrombophilia	11 (9%)	11 (9.2%)	4 (12.1)	5 (13.9)
Cancer	33 (27%)	36 (30.3%)		
Bedridden	34 (27.9%)	43 (36.1%)	8 (24.2)	12 (33.3)
Traumatism	14 (11.5%)	18 (15.1%)	0 (0.0)	2 (5.6)
Surgery	8 (6.6%)	11 (9.2%)	3 (9.1)	5 (13.9)
Oral contraception	6 (4.9%)	10 (8.4%)	0 (0.0)	2 (5.6)
Status at entry				
Iliofemoral	22 (18%)	12 (10.1%)	12 (36.4)	4 (11.1)
Femoro-popliteal	72 (59%)	80 (67.2%)	16 (48.5)	28 (77.8)
Popliteal	28 (23%)	27 (22.7%)	5 (15.1)	4 (11.1)
D-dimer (median)	868 (244–13,460)	860 (275–9942)	1050 (430–13,460)	1040 (303–9942)
Last D-dimer[a] (median)	253 (100–1678)	240 (110–1672)	490 (190–1563)	420 (110–1672)
Last D-dimer <235	54 (45.8%)	53 (49.5%)	7 (21.2%)	8 (25.8%)
Time of evolution				
<48 h	30 (24.6)	31 (26.1)	12 (36.4)	12 (33.3)
3–7 days	70 (57.4)	66 (55.5)	16 (48.5)	22 (61.1)
>7 days	22 (18)	22 (18.5)	5 (15.1)	2 (5.6)

[a] Last D-dimer was measured 30 days after treatment. Data are missing in 16 patients (four in the AVK group and 12 in the LMWH group).

CI: −9.3% to−0.46%). This difference was also observed in the sub-group of 69 patients with cancer (0% vs. 15.16%; $p = 0.015$; 95% CI: −7.6% to−0.58%).

Analysis of risk factors for DVT

From the univariate analysis of the demographic and medical characteristics listed in Table 3 the age was associated with greater odds of DVT and the reduction of D Dimer with lower odds of DVT. In contrast, the venous segment affected, the time of evolution or the D-dimer level after treatment was not associated with recurrence. Excluding the DVT that occurred in the first 12 days, while both groups were treated with LMWH, the factors associated with greater odds of DVT were cancer (4.4, 95% CI: 1.02–18.9; 0.047), previous surgery (8.1, 95% CI: 1.78–37.16; 0.007) and the lower reduction of D-dimer (1.0002, 95% CI: 1.0001–1.0003; 0.006). There was a tendency of higher risk of DVT in patients treated with AVK (7.18, 95% CI: 0.87–59.3; 0.07).

In the multivariate analysis, the risk factors independently associated with greater odds of DVT were the age of the patient and a lower reduction of D-dimer from baseline.

Clinical examination

In both groups, response to treatment was good and resolution of symptoms and clinical signs was quick. This was noticeable from the first re-evaluation after 1 month of therapy. On completion of the treatment period, the clinical appearance was similar in the LMWH and AVK groups: oedema (13.4% vs. 13.9%), local tenderness or pain (0% vs.

Table 2 Recurrent venous thrombo-embolism

	6 Months		1 Year	
	LMWH $N = 119$	LMWH/AVK $N = 122$	LMWH $N = 119$	LMWH/AVK $N = 122$
New episodes of PE	4 (3.4%)	3 (2.5%)	4 (3.4%)	3 (2.5%)
Recurrent DVT	1 (0.8%)	4 (3.3%)	2 (1.7%)	10 (8.2%)
Total recurrent VTE[a]	5 (4.2%)	7 (5.7%)	6 (5.0%)	13 (10.7%)

[a] There was a trend in the reduction of recurrences of DVT at 12 months in patients treated with tinzaparin (Fisher's exact test $p = 0.15$).

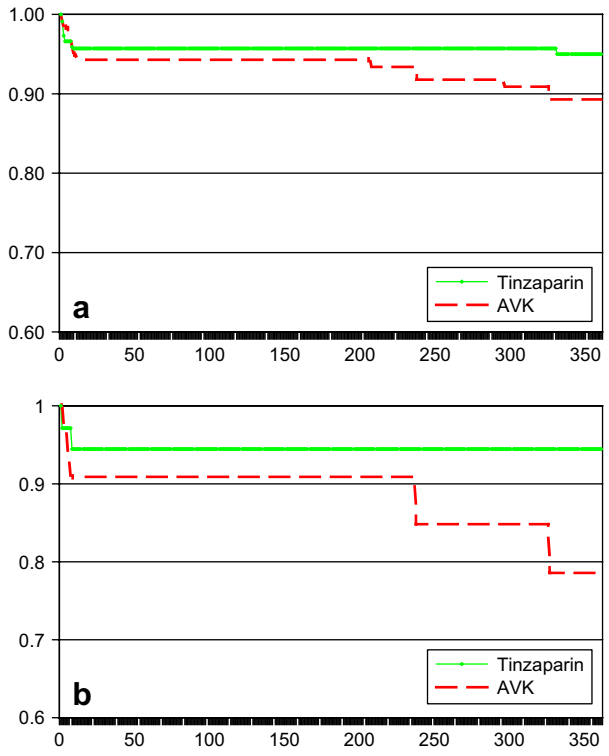

Figure 1 (a) Cumulative incidence of recurrent venous thrombo-embolism in the treatment groups. There was a non-significant reduction in the recurrence of venous thrombo-embolism in the tinzaparin group as compared with the oral-anticoagulant group (log-rank test $p = 0.11$). Estimates after cessation of the anticoagulant treatment (day 180) in the treatment groups. There was a significant reduction in the tinzaparin group (log-rank test $p = 0.03$). (b) Kaplan–Meier estimates the probability of recurrent venous thrombo-embolism in patients with cancer in the treatment groups. There was a non-significant reduction in the tinzaparin group (log-rank test $p = 0.06$). Excluding the patients with symptoms of pulmonary embolism that occurred on the day of randomisation (one per group) the difference was significant (log-rank test $p = 0.018$).

1.6%), respectively. No fractures or symptoms of severe osteoporosis were reported during the treatment period.

Degree of thrombus regression

We compared the ultrasound changes between treatment groups at baseline, at 6 months and upon conclusion of the observation phase (1 year). Differences in complete resolution of the clot were observed after 6 months (58–47.5% vs. 87–73.1%; $p < 0.001$) and 12 months (83–69.2% vs. 107–91.5%; $p < 0.001$) between AVK and LMWH groups, respectively. A comparison of these findings is presented in Table 4, which shows the advantage of tinzaparin over acenocoumarol.

The ultrasound assessment of the whole sample at 6 months showed that five (5.2%) of 96 patients with incomplete re-canalisation and three (2.1%) of 145 with complete re-canalisation developed a new DVT after cessation of anticoagulant treatment ($p = 0.27$). None of the 71 patients with complete re-canalisation and low D-dimer level exhibited new DVT after discontinuation of anticoagulant (0% vs. 5.2%; $p = 0.11$).

The affected limbs were examined for the presence of venous reflux in 116 patients in the AVK group and 117 patients in the LMWH group as part of routine ultrasound scanning at 12 months. Veins were considered to be competent in 22 (19%) patients in AVK and in 69 (59%) patients in LMWH groups, respectively ($p < 0.001$).

Bleeding

Three of 122 patients in the AVK group (2.5%) and one of 119 patients who received tinzaparin (0.8%) had major bleeding ($p = 0.6$). Major bleeding was associated with an INR of more than 3.0 in two patients in the AVK group. There were no fatal bleeding events. Minor bleeding events were not registered.

Discussion

This study indicates that after initial short-term management with LMWH, long-term LMWH is, at least, as effective as long-term vitamin-K antagonist therapy in patients with acute proximal venous thrombosis. It is possible that with a larger sample size, the difference may achieve statistical significance. The findings of our study are supported by previous research and the literature.[2–8,15,16]

The possible advantage of tinzaparin over AVK disappeared when we analysed the patients without cancer. The meta-analyses of a number of small studies that included, primarily, patients without cancer and used prophylactic doses of LMWH for extended treatment rather than full therapeutic doses found a non-significant reduction of approximately 30% in the risk of recurrent VTE favouring LMWH.[9,17] A more recent and larger study also failed to find a significant difference between LMWH given at full dose and AVK.[18] Overall, LMWH does not appear to offer any measurable efficacy or advantage over standard treatment with AVK in patients without cancer.

The statistically significant difference favouring LMWH over AVK in all patients receiving treatment comes mostly from studies[10–13] that included cancer patients. In our study, time-to-event analysis in patients with cancer, identified at the time of entry, also suggests that long-term LMWH may be more effective than traditional therapy. We cannot rule out that the two patients (one from each group) who developed symptoms of pulmonary embolism on the day of randomisation were new occurrences. When we excluded these recurrences from the analysis, the differences between groups in the cancer population reached statistical significance.

It has been reported[18] that patients treated with long-term LMWH have recurrent events earlier after cessation of therapy compared with AVK, even though persistent excessive VTE events (true rebound) do not occur.[18,19] The results could in part be due to the different proportion of patients in the two groups who received prolonged treatment beyond 3 months without a standardisation of treatment duration after the initial 3 months. In addition, the

Table 3 Univariate associations between medical characteristics and recurrence of venous thrombo-embolism

Characteristic	Patients	DVT *n* (%)	Odds ratio (95% CI)	*p*-Value
Age (year ± SD)	60.1 SD 16.9	19	1.038 (1.0004–1.077)	0.0478
Sex				
Female	107	8 (7.5)	1.00	0.83
Male	134	11 (8.2)	1.107 (0.43–2.86)	
Risk factors				
Thrombophilia				
No	219	17	1.00	0.82
Yes	22	2	1.19 (0.26–5.52)	
Cancer				
No	172	10	1.00	0.066
Yes	69	9	2.43 (0.94–6.27)	
Bedridden				
No	164	11	1.00	0.33
Yes	77	8	1.61 (0.62–4.19)	
Trauma				
No	209	15	1.00	0.305
Yes	32	4	1.85 (0.57–5.96)	
Surgery				
No	222	16 (7.2)	1.00	0.19
Yes	19	3 (15.8)	2.41 (0.63–9.16)	
Status at entry				
Venous segment				
Popliteal	55	5	1.00	0.88
Iliofemoral	34	3	0.97 (0.22–4.33)	
Femoral	152	11	0.78 (0.26–2.36)	
Last D-dimer	407 ± 496	225	1.0001 (0.9993–1.0009)	0.84
Reduction D-dimer	−1474 ± 3000	225	0.999 (0.9998–1.00)	0.018
Time of evolution				
>7 days	44 (18.3)	5 (11.4)	1.00	0.33
<48 h	61 (25.3)	3 (4.9)	1.086 (0.174–6.79)	
3–7 days	136 (56.4)	11 (8.1)	2.41 (0.53–11.05)	
Treatment				
Tinzaparin	119	6	1.00	
Acenocoumarol	122	13	2.25 (0.82–6.12)	0.11

Table 4 Ultrasound changes between treatment groups at 6 months and upon conclusion of the observation phase

		6 Months		1 Year[a]	
		LMWH $N = 119$	AVK $N = 122$	LMWH $N = 117$	AVK $N = 120$
Thrombus regression[b]	Complete	87 (73.1%)	58 (47.5%)	107 (91.5%)	83 (69.2%)
	Incomplete	32 (26.9%)	64 (52.5%)	10 (8.5%)	37 (30.8%)
Degree of occlusion[c]	Occluded	2 (1.7%)	5 (4.1%)	1 (0.8%)	2 (1.7%)
	Severe	1 (0.85%)	1 (0.8%)	0 (0%)	0 (0%)
	Moderate	3 (2.5%)	21 (17.2%)	2 (1.7%)	9 (7.5%)
	Mild	26 (21.85%)	37 (30.3%)	7 (6.0%)	26 (21.6%)
	Total re-canalisation	87 (73.1%)	58 (47.6%)	107 (91.5%)	83 (69.2%)

[a] Four patients died before the ultrasound evaluation.
[b] Regression of the thrombus was different in the LMWH than in the AVK group at 6 and 12 months, respectively (Fisher's exact test $p < 0.001$).
[c] Total re-canalisation was more frequent in the LMWH group than in the AVK group at 6 and 12 months (chi-square test $p < 0.001$). Grouping total re-canalisation and mild occlusion, differences were statistically significant at 6 months (Fisher's exact test $p < 0.01$), but there was only a trend at 12 months (Fisher's exact test $p = 0.051$).

possibility that very low LMWH doses used in some trials for the long-term treatment of symptomatic VTE should also be taken into account.[19] With these differences in the clinical trials, it is difficult to extract a uniform clinical conclusion from these studies. However, our findings after 6 months of treatment showed a significant ($p = 0.03$) excess of recurrent symptomatic VTE outcomes during follow-up in the AVK group compared with LMWH.

A possible drawback is that a double-blind study was not feasible due to the different routes of administration of the two drugs and the need for regular dose adjustment in the AVK group. However, the ultrasonographic evaluations were performed blindly.

This study also showed that not only can tinzaparin be used safely and effectively to treat DVT at home over the long term but also that its ability to re-open thrombosed veins is better than that of acenocoumarol. A higher degree of re-canalisation was shown with ultrasonography in the patients assigned to undergo LMWH therapy as compared with the patients assigned to undergo treatment with coumarin. These results are in concordance with other published studies where thrombus regression was more prominent in the LMWH group.[2,8,15] The percentage of patients with complete and substantial re-canalisation in the AVK group was at least similar to other studies.[2,5,8,15,16] In fact, both therapeutic regimens were proved to be effective in preventing progression of thrombi and allowing re-canalisation of the affected veins. However, thrombolysis appears more extensively in the LMWH than in the AVK group. It is interesting to note that the incomplete re-canalisation after 6 months of treatment with D-dimer levels increased and was likely to be associated with recurrence of DVT. This finding could have therapeutic implications in the management of the disease.[20,21]

The improved re-canalisation could explain, partly, the difference of recurrence of DVT after treatment between both groups. Cancer is also another factor that could explain this excess of recurrence in the AVK group. In other study, the incidence of DVT was higher in the AVK group after treatment period.[12] In addition, when we excluded the patients with cancer in our study, we did not find any difference. Whether the use of full LMWH dose for the whole treatment period in patients with cancer had any influence in the percentage of recurrence after treatment needs to be confirmed.

We also found that earlier re-canalisation resulted in less valve incompetence. Reflux in the veins was significantly different when comparing the two treatments. This is in agreement with other authors who demonstrated a significantly lower rate of reflux in the veins of patients treated with LMWH,[8] but different from others.[15] Our findings, although the sample size was not sufficient, suggest that LMWH may reduce the risk of late recurrence after treatment in the 6-month follow-up period. It also suggests that LMWH may reduce the risk of the late sequelae of DVT. However, in our population, without previous history of ipsilateral DVT, the 12-month follow-up period used in this study is too short to reflect the true development of clinical post-thrombotic syndrome.[22]

Since the majority of proximal DVTs require a 6-month therapy, we excluded distal DVTs from our study that might respond to a shorter therapy. In addition, we examined the period after cessation of the therapy. To our knowledge, only four randomised trials used LMWH for 6 months.[8,11,13,15] In two studies that included cancer patients only, there was no follow-up after the treatment period.[11,13] In other two studies with a follow-up period till 1 year, LMWH was administered for 6 months[8,15]; however, only in one of them the initial dosage of LMWH was maintained during the whole study.[15] Results from these studies were in favour of LMWH.

In conclusion, our study suggests that a single fixed dose of tinzaparin administered at full therapeutic dosage for a period of 6 months is at least as effective and safe as the usual AVK treatment for preventing recurrent VTE. Subanalysis shows that tinzaparin is preferred in patients with cancer along with VTE.[11,12] Tinzaparin with a sub-cutaneous injection once daily is more effective than AVK in achieving re-canalisation of veins affected by thrombus.

Conflicts of Interest

Esteve Colomé works in Laboratorios LEO Pharma, SA, and participated in the writing of the manuscript. None of the other authors had any financial interest or arrangements of concern with the medications that might pose a conflict of interest.

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